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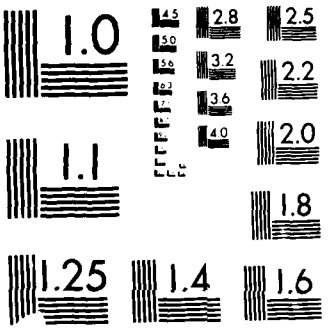

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STUDY OF THE EFFECTS OF DRUGS UPON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS

Subtitle: EVALUATION OF PULMONARY AND CARDIOVASCULAR EFFECTS OF DRUGS OF MILITARY INTEREST

FINAL REPORT

by

Robert W. Caldwell

Clinton B. Nash

June 1, 1986

(November 1, 1982 - April 15, 1986)

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701-5012

Contract No: DAMD17-83-C-3011

University of Tennessee Center for the Health Sciences
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1. Study of the cardiopulmonary actions of WR-6026 and Primaquine was completed and submitted 2 March 1984.
2. Study of the Determination of the Involvement of Histamine in the Blood Pressure Response to Liposome was completed and submitted 15 March 1985.
3. Study of the Cardiovascular and Pulmonary Effects of Pyridostigmine Bromide in the Dog: Correlation with Blood Cholinesterase Inhibition was completed and submitted February 1986.

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FOREWORD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

Period I (1 November 1982 - 31 December 1983)

1. Pilot experiments were performed to define the cardiopulmonary actions of WR-6026 and primaquine. A maximum tolerated dose-rate of WR-6026 of 4 μmoles/kg/min was established. Alterations in ECG patterns were prominent and marked increases in P-R and Q-T intervals were noted. A minimum effective dose-rate of WR-6026 was found to be 0.5 μmoles/kg/min causing only slight rises in systolic blood pressure, LV dP/dt, respiratory rate, and minute volume.

Primaquine was evaluated at dose-rates of 0.5 - 1.75 μmoles/kg/min. The dose-rate of 1.75 μmoles/kg/min had been previously shown to be the maximum tolerated dose-rate causing severe cardiopulmonary changes but did not result in death.

2. The protocol to study the Cardiovascular and Pulmonary Effects of WR-6026 · 2 HCl vs. Primaquine · 2 H_3PO_4 was written and submitted on 5 August 1983. A range of dose-rates for WR-6026 was set at 1.0 - 4.0 μmoles/kg/min. A range of dose-rates for primaquine was set at 0.5-1.75 μmoles/kg/min. The following parameters would be monitored at ten minute intervals, beginning 30 minutes prior to drug infusion, continuing for 20 minutes during drug infusion, and for 100 minutes after infusion:

A. Cardiovascular Measures

1. arterial blood pressure -- continuous
2. left ventricular pressure -- continuous
   a. dP/dt -- continuous
   b. left ventricular end diastolic pressure -- continuous

3. electrocardiogram -- at 10-minute intervals: all six limb leads will be recorded at 25 mm/sec and strips at 100 mm/sec for analysis

4. heart rate -- continuous: by cardiotachometer

5. pulmonary vascular

   a. pulmonary artery pressure -- continuous

   b. pulmonary wedge pressure -- at 10-minute intervals

   c. cardiac output -- at 10-minute intervals

   d. pulmonary vascular resistance -- calculated at 10-minute intervals

B. Pulmonary Ventilatory Measures

1. Airways differential pressures

   a. air flow -- signal integrated by preprogrammed computer

   b. transpulmonary pressure (bronchial vs esophageal) -- signals utilized by preprogrammed computer

2. Airways integrated measure -- tidal volume, continuous

3. Airways computer measures

   a. compliance -- continuous = $\Delta V/\Delta P$

   b. resistance -- continuous = $\Delta P/\Delta F$

4. Respiratory rate -- continuous

C. Hematological Measures - (-30 and 0 minutes only)

1. Blood P_{CO2} -- arterial and venous

2. Blood P_{O2} -- arterial and venous

3. Blood pH -- arterial and venous

4. Hematocrit -- central venous

3. The entire experimental series for WR-6026 and primaquine was performed. It was found that a higher dose-rate of WR-6026 was tolerated than for primaquine, 4.0 vs. 1.75 μmoles/kg/min. The dose-response curves for cardiopulmonary effects were of similar slope. Death from WR-6026 resulted

from gradual cardiac function depression; primaquine produced death by a primary action on heart rhythm. At low dose-rates WR-6026 caused a slight increase in respiratory rate and minute volume. Primaquine, at low dose-rates, had no perceptable effect on respiratory function. Left ventricular dP/dt was depressed slightly and transiently, P-R interval was modestly increased.

Period II (1 January 1984 - 31 December 1984)

1. A report of the Cardiovascular and Pulmonary Effects of WR-6026 · 2 HCl vs. Primaquine Diphosphate was completed and submitted 2 March 1984. WR-6026 produced prominent depression of cardiac contractility, elevated respiratory rate and depressed airways resistance. Primaquine showed far less prominent actions on cardiovascular, hemodynamic, and pulmonary variables. Both agents slowed A-V nodal and ventricular conduction velocity; Primaquine, however, may produce dangerous ventricular arrhythmias.

2. The protocol to determine the Involvement of Histamine in the Blood Pressure Responses to Liposome Carriers was written and submitted on 12 September 1984. Since liposome carrier suspension produces an arterial hypotension when given intravenously, prior treatment with compound WR-149, 024 would be studied to determine if it would stabilize histamine-containing cells and antagonize factors which induce histamine release to reduce this hypotension. If release of histamine from body stores is responsible for the hypotension to liposome injections, a tachyphylaxis should develop as histamine stores are depleted. In dogs with chronically indwelling catheters to measure systemic and pulmonary arterial pressures, it could be determined if repeated i.v. bolus injections of a given amount of liposome carrier suspension yield systemic or pulmonary arterial pressure responses which are progressively smaller.

3. Preliminary experiments were performed on the Effects of Carrier Liposomes on the Canine Cardiovascular System and the results were submitted on 27 June 1984. The liposome suspension produces an arterial hypotension when given intravenously. Prior treatment with WR-149,024 appeared to reduce the development of hypotension to liposome infusion. Since one of the properties of WR-149,024 is to stabilize histamine containing cells and antagonize factors

which induce histamine release, then histamine is probably involved in this hypotension.

Period III (1 January 1985 - 15 April 1986)

1. The Study of the Determination of the Involvement of Histamine in the Blood Pressure Response to Liposome was completed and submitted 15 March 1985. Bolus i.v. injections of 1,2, and 3 ml of liposome into each of two anesthetized beagles did not produce a change in arterial pressure. However, in one beagle, volumes of 4 and 5 ml of liposome carrier produced a systemic and pulmonary hypotension. Therefore, relatively large volumes of liposome suspension injected as a bolus are required to reduce arterial blood pressure. The fact that injection of liposomes caused a fall in pulmonary artery pressure is not entirely consistent with the concept of histamine release by liposomes, since histamine is a vasoconstrictor in the pulmonary vascular bed of the dog. However, if the site of histamine release is passed (the pulmonary resistance vessels), enough histamine may not reach the pulmonary vessels through return of blood to produce vasoconstriction. The fall in pressure in the pulmonary circuit might be passively due to a transient reduction in venous return.

2. A protocol to study the Cardiovascular and Pulmonary Effects of Pyridostigmine Bromide in the Dog: Correlation with Blood Cholinesterase Inhibition was written and submitted on 19 June 1985. The proposed studies would determine and correlate the cardiovascular and pulmonary actions of graded intravenous doses of pyridostigmine Br in the anesthetized dog. The range of doses to be studied would be from that producing a small but definite effect upon cardiovascular and/or pulmonary function, to a dose which produces severe changes in cardiopulmonary function, just short of death. A dose producing effects intermediate to these extremes would also be used. In addition, the studies would correlate plasma acetylcholinesterase activity with cardiovascular and pulmonary function before, during, and after administration of pyridostigmine.

3. The Study of the Cardiovascular and Pulmonary Effects of Pyridostigmine Bromide in the Dog: Correlation with Blood Cholinesterase Inhibition was completed and submitted February 1986. It was found that heart rate was reduced in response to pyridostigmine in a dose related fashion. It, in some ways, mirrored the rise in P-R interval caused by this drug; possibly because both these actions were due to enhancement of vagal function; the fall in diastolic pressure correlated with the fall in heart rate. Even in spite of reductions in heart rate, cardiac output was maintained or even augmented during the infusion period. Stroke volume rose in a dose-related fashion during drug infusion. This rise in cardiac output during drug infusion was associated with an increase in cardiac contractility, LV dP/dt. Rises in both cardiac contractility and output corresponded temporally to the increases in systolic and arterial pulse pressures.

In the pulmonary vascular bed, pyridostigmine infusion increased arterial pressure at all dose-rates. Vascular resistance was also elevated in a parallel fashion. It appeared that a strong direct pulmonary vasoconstriction occurred, since cardiac output was maintained or even augmented during this period. Since pulmonary wedge pressure was also elevated, this suggested that an active constriction of the pulmonary veins and/or capillaries occurred.

Respiratory rate was variably elevated during the mid and high dose-rate infusion, and during this period, the average tidal volume was reduced by about 25%. Minutes volume, the product of respiratory rate times tidal volume, was elevated by both the mid and high dose; the greater contributor to this response and variability was rate. Minute volume and respiratory rate were maintained at a level higher than control for most of the observation period. Airway resistance was markedly elevated by the high dose of pyridostigmine. The rise in airways resistance was mirrored by a drop in airways compliance;

but these two responses are probably not causally related.

Cholinesterase activity in blood was reduced in a dose-related fashion by pyridostigmine. Reduction in activity was greatest at the end of drug infusion. There was a partial (10-20%) recovery of enzyme activity over the 10 minute period immediately after the end of drug administration. A maintained reduced state of inhibition was then apparent for the rest of the experimental period. The partial recovery may have been due to a redistribution of pyridostigmine from blood to other body compartments. All of the cardiopulmonary changes can be related to the effects of Pyridostigmine directly on cholinesterase activity or through effects subsequent to cholinesterase inhibition. Heart rate, which was marked reduced, and airway resistance, which was markedly elevated, appear to be the variables most affected. Other changes in cardiovascular and pulmonary function may be considered as consequences of these primary events.

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